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A Review on Promising Natural Agents Effective on Hyperlipidemia

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Abstract

Hyperlipidemia is a prevalent disease and a major component of the metabolic syndrome resulting from various factors. This disease increases morbidity and mortality when combined with other prevalent diseases such as diabetes mellitus, hypertension, and cardiovascular diseases. The side effects of the current lipid-lowering drugs have increased the tendency to move toward traditional and alternative treatments. Epidemiological observations indicate that using alternative treatments, consumption of medicinal plants, diet, and consumption of fruits have had satisfactory results on the effects of hyperlipidemia in many societies. It should be noted that in majority of societies, even developed countries, the tendency toward eating lipid-lowering medicinal plants has increased extensively. Using these plants especially when common remedies cannot control the disease is significant. Although consumption of medicinal plants by hyperlipidemic patients may show improvement in disease state, drug interaction and side effects may cause complications in disease control. Therefore, in this review, apart from introducing some of the reliable plants effective in inhibition and decrease of hyperlipidemia, the possibility of their intoxication and drug interaction is also presented.

Keywords

hyperlipidemia, lipid, medicinal plants

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Nowadays, cardiovascular complications are considered as the main factors of morbidity and mortality. Globally, the number of deaths from cardiovascular diseases has increased from 14.4 million in 1990 to 17.5 million in 2005, and it is estimated to be about 20 million in 2015.[1] Some circulating agents such as low-density lipoprotein free radicals, homocysteine, and nicotine are also considered as leading factors. Morbidity and mortality increase when combined with other prevalent diseases such as diabetes mellitus and hypertension.[2]

The formation of atherosclerotic plaque involves accumulation of low-density lipoprotein in intima, low-density lipoprotein oxidation, uptake of oxidized low-density lipoprotein by macrophage scavenger receptors, influence of macrophages on foam cells, and stabilization of plaque. In all steps of atherosclerosis, inflammatory cytokines are involved and make this process a chronic inflammatory disease.[3]

When the blockage of the coronary arteries reaches more than 75%, usually the symptoms of angina will gradually appear. Blood clot usually develops on the irregular surfaces of arteries, which then may become detached, thus blocking the downstream blood flow. Heart attacks and strokes are usually caused by such blood clots. Moreover, the atherosclerotic blood vessels are generally weak and can burst. The best treatment in diseases such as atherosclerosis is prevention. Therefore, conventional medical approaches generally focus on lifestyle changes, such as reduction in the consumption of saturated fats, quitting smoking, and aerobic exercise. Drugs are also used to lower cholesterol levels or blood pressure; however, most of them possess considerable side effects.[4]

Using alternative treatments, especially medicinal plants and their complements, to treat different diseases such as hyperlipidemia,[5-7] diabetes,[7,8] and cardiovascular diseases[9-12] has increased over the recent decades in majority of countries worldwide. One of the important problems faced by doctors and also users of medicinal plants is lack of enough information in the field of drug safety and its effect on disease.[13,14]

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Fortunately, extensive studies have been done on the effectiveness of medicinal plants used in traditional medicine over the 30 past years and some of their efficiencies and deficiency have been recorded.[15-18]

This review was therefore aimed to introduce some promising medicinal plants effective in the prevention or treatment of hyperlipidemia, apart from presenting the possibility of their intoxication and drug interaction.

Lipid-Lowering Medicinal Plants

Different remedies are used to treat hyperlipidemia in traditional medicine in which the role of medicinal plants is significant. Recent researches performed on medicinal plants and food supplements used in traditional medicine indicate that compounds present in them including food fibers, vitamins, flavonoids, sterols, and other antioxidant compounds can lower lipids, inhibit low-density lipoprotein oxidation, eliminate oxygen free radicals, and possibly improve this disease by having an effect on the immune system and improving metabolic disorders of the body.[19-22]

Cynara cardunculus (Artichoke)

In the early 20th century, French scientists stated this plant as liver and bile stimulator. Leaves of artichoke are used as diuretic to stimulate kidneys and as bile stimulator to release the flow of bile from the liver. Italian scientists used to prescribe the cynarin compound (effective substance of artichoke) to stimulate the liver and gallbladder and to treat elevated cholesterol.[23] Use of artichoke leaves stimulates bile production and results in dyspeptic problems being treated. There are no valid evidences indicating that leaves of this plant treat dyspeptic problems directly.[24] A number of animal studies suggest that artichoke leaves inhibit cholesterol synthesis in liver cells and also protect the liver from damages caused by chemical toxins.[25] According to a study performed on 143 patients with high cholesterol, leaves of artichoke improved the level of cholesterol significantly.[26] In this randomized, double-blind, placebo controlled, multicenter trial, the initial total cholesterol of patients was equal to or more than 280 mg/dL. Patients received 1.8 mg/day artichoke dry extract ($n = 172$) or placebo ($n = 171$) for 6 weeks. Total cholesterol was decreased 18.5% in the drug group versus 8.6% decrease in the placebo group; low-density lipoprotein cholesterol by 23% versus 6%; and low-density lipoprotein to high-density lipoprotein ratios by 20% versus 7%. Compounds present in the leaf of artichoke like cynarin and luteolin may play a significant role in reducing the synthesis of cholesterol as well as its total level.[26]

Dosage. According to Germany's Commission E, 6 g of the dried herb or its equivalent (totally 3 times per day) is the optimal dose to treat *dyspepsia*. However, the optimal dose for hyperlipidemia is not mentioned.[27]

Toxicity. No side effect has been observed in using leaves of artichoke so far, but since investigations in this regard are not complete, pregnant or nursing women are recommended not to use it. Also, young children or people with severe liver or kidney disease and individuals with gallstones should use the leaves with caution. Individuals with allergies to artichoke or similar plants (*Asteraceae* family) such as arnica or chrysanthemums should avoid using artichoke or cynarin preparations.[27]

Medicago sativa (Alfalfa)

In traditional medicine, *Medicago sativa* is used as a dietary supplement, antidiabetic, antihyperlipidemic, and anti-allergen. It is also used to treat menstrual disorders, gastrointestinal tract disorders, kidney and urinary tract problems, burns, and arteritis. This plant is used as a dietary supplement, thanks to it containing high amounts of β-carotene and vitamins, including B, C, E, and K. Researches have suggested that seeds of *Medicago sativa* have the ability to decrease the blood cholesterol level in laboratory animals. Using seeds of this plant in monkeys for 1 year not only suggested no side effects but also reduced the blood cholesterol level.[28]

In this study in which the effects of alfalfa on aortas from cynomolgus monkeys with diet-induced atherosclerosis were evaluated, alfalfa resulted in varied degrees of regression of lesions. The results also showed that mean hydroxyproline as well as total glycosaminoglycan concentration in aortas was correlated with the severity of the lesions ($P < .05$). These observations suggest that connective tissue components are intimately involved in remodeling the aorta during regression of diet-induced atherosclerosis.[28]

Laboratory studies have reported the presence of plant estrogens in this plant that may be useful to treat menstrual disorders. This plant is also used to treat pollinosis but clinical studies have not determined the effectiveness of this plant in the treatment of this disease.[28,29]

Dosage. In traditional medicine, 1 to 2 spoons of the powder of leaves or plant seeds that are infused in boiled water for 10 to 20 minutes are used. Pill or capsule of the plant should be used according to the instruction of the manufacturer.[29]

Restrictions. Due to estrogenic effects existing in some compounds of this plant, pregnant and nursing women or children should not use this drug.[29]

Drug Interaction. Due to high amount of vitamin K in this plant, the effects of wafarin in individuals who use this plant may decrease if it is used along with warfarin.[30]

Toxicity. Powder of plant and seeds of *Medicago sativa* contain L-cavanin, a substance that may cause disorder in blood cells and lead to the splenomegaly.[30]

Trigonella foenum graecum L (Fenugreek)

In traditional medicine, *Trigonella foenum graecum* L is prescribed to treat diseases like diabetes, high cholesterol, bronchitis, constipation, dyspepsia, and renal problems. Studies conducted on laboratory animals and clinical studies suggest that this plant decreases the level of blood sugar in diabetic patients and lowers blood cholesterol. This plant like other food products containing high fiber can be useful to treat constipation. Twenty-five individuals with type 2 diabetes mellitus, in 2 drug (1 g of the extract per day) and placebo groups, were compared in a 2-month period. The level of blood sugar decreased significantly in the drug group compared with the placebo group, and the level of triglyceride decreased and high-density lipoprotein level increased in this group.[30,31]

Other animal and human studies have also suggested that fenugreek ameliorates blood triglycerides, total cholesterol, and low-density lipoprotein. It also prevents low-density lipoprotein from oxidation, which is one the major components of atherosclerosis induction. These effects have been attributed to the plant's sapogenins and phytoestrogens. Sapogenins have been shown to increase biliary cholesterol excretion, and phytoestrogens indirectly increase thyroid hormones.[31]

Dosage. The usual dosage is 5 to 30 g of the plant seed powder 3 times per day in the meal time.[31]

Toxicity. This plant has mild gastrointestinal tract stimulatory effect, if it is used in high dose. No toxic effect was observed in animal studies as a result of eating this plant. The extract obtained from seed of *Trigonella foenum graecum* L has created the stimulatory effect on uterus of guinea pig. For this reason, pregnant women are recommended to avoid eating this plant, and it should not be used by children and patients with renal and liver diseases.[30]

Drug Interaction. Seed of *Trigonella foenum graecum* L intensifies the effect of insulin or other blood sugar-lowering drugs due to blood sugar lowering property.[30]

Allium sativum L

Allium sativum L (garlic) is used in the treatment of an extensive range of diseases. The aromatic compound alliin is one of the most important compounds that exist in *Allium sativum* L. When garlic is cut or pressed, an enzyme named Alinase affects alliin, transforming it to allicin, which is the main factor of the strong odor of the garlic.[32] Today, garlic is used to treat gastrointestinal tract disorders, asthma, diabetes, cardiovascular diseases, hypercholesterolemia, common cold, and high blood pressure.[33] Although it is stated that using this plant decreases cholesterol and blood pressure, there are contradictive scientific evidences in this regard. Although some studies performed over the 1980 to 1990 decades suggested that garlic can decrease the blood cholesterol level, some more recent studies have shown contrary results.[4,33,34]

In a clinical study, taking the garlic capsules for 12 weeks, the compound was able to decrease cholesterol and low-density lipoprotein significantly in 46 patients with high blood cholesterol.[35] In this clinical trial, following 12 weeks of garlic supplement ($n = 22$), the total cholesterol and low-density lipoprotein cholesterol levels significantly decreased, while these parameters were not statistically changed in the placebo group ($n = 24$). In this study, no significant difference was observed in triglycerides or in low-density lipoprotein/high-density lipoprotein ratio between groups. The authors concluded that enteric-coated garlic supplements, with 9.6 mg allicin-releasing value, has potential to ameliorate the lipid profile of patients with mild to moderate hypercholesterolemia when they are recommended to have low-fat diet. Taken with other evidence, the ability of garlic extract for reduction of hypercholesterolemia might be attributed to allicin bioavailability, that is, greater anticholesterolemic efficacy might be evident at a higher allicin level.[35]

Effect of Garlic on Atherosclerosis and Aorta Elasticity. Primary information has suggested that garlic may be effective in inhibiting atherosclerosis formation, which is an important factor of cardiovascular diseases. It has been reported that garlic decreases formation of the atherosclerosis plaque in laboratory animals.[4] In a clinical study performed on 152 individuals, using 900 mg of garlic powder daily for 4 years decreased formation of the atherosclerosis plaques significantly.[36] In other clinical study performed on 200 individuals, the positive effect of the garlic in decreasing the formation of atherosclerosis plaque was observed.[37] In this study, healthy adults ($n = 101$; age = 50 to 80 years, matched with the same number in the control group) were administered 300 mg/day of garlic powder for at least 2 years. Pulse wave velocity, elastic vascular resistance, and pressure were used to measure the elastic properties of the aorta. The heart rate, blood pressure, and lipid profile were similar in the 2 groups. The pulse wave velocity ($P < .0001$) and elastic vascular resistance ($P < 0.001$) were lower in the garlic group than in the control group. Pulse wave velocity showed significant positive correlation with systolic blood pressure and age. Analysis of covariance and multiple regression analyses demonstrated that age and systolic blood pressure were the most important determinants of pulse wave velocity and that the effect of garlic on pulse wave velocity was independent of confounding factors. The authors concluded that garlic intake would protect the effect of the elastic properties of the aorta related to aging in humans.[37]

Dosage. The usual consumed dose of garlic powder is 900 mg daily that contains 1.3% alliin, that is, about 12 mg alliin daily. The most suitable proposed dose that has been obtained over clinical studies is about 10 mg alliin, which produces approximately 4 to 5 mg allicin. Using 1 to 7 g of alliin-free garlic daily has properties of fresh garlic.[36]

Toxicity. Using 2000 mg/kg body weight for 6 months created no negative phenomenon in rats. The most common side effect of

garlic is its undesired odor. Other side effects are observed rarely. For example, a study was performed on 1997 individuals who used normal dose of odorless garlic for 16 weeks. Nausea was seen in 6% of them, vertigo in about 1.3% (may be due to blood pressure decrease), and allergy in 1.1%. Limited reports also have been stated about headache, vertigo, hyperidrosis, and tympanites.[32]

Glycine max (Soybean)

Soya as a food product rich in protein is used in Asia and as free-cholesterol meat in traditional food of American people. The American Food and Drug Administration has allowed producers of food products containing soybean to use the healthy heart label on their products. In traditional medicine, soybean has been used to decrease blood cholesterol and also as an anticancer and anti-osteoporosis drug.[32]

The Therapeutic Consumption of Soybean. Several studies have suggested that soybean can decrease low-density lipoprotein in the blood. In a study performed on 38 individuals with high blood cholesterol, soybean decreased blood cholesterol and improved the low-density lipoprotein/high-density lipoprotein ratio. In this meta-analysis study the effect of soy protein intake was evaluated on serum lipid profile of hyperlipidemic patients. In most of the evaluated trials, the intake of cholesterol, fat, saturated fat, and energy was nearly equal in the control and soy-containing diet groups. The average soy protein intake was 47 g/day. Consumption of soy protein was associated with average changes in serum lipid profile as follows: a decrease of 23.2 mg/dL or 9.3% in cholesterol, a decrease of 21.7 mg/dL or 12.9% in low-density lipoprotein cholesterol, a decrease of 13.3 mg/dL or 10.5% in triglycerides. The ingestion of soy protein was associated with a nonsignificant 2.4% increase in serum concentrations of high-density lipoprotein cholesterol. The author concluded that consumption of soy protein is beneficial in hypercholesterolemic patients. Thus, soy protein rather than animal protein was able to significantly decrease the serum concentrations of triglycerides, total cholesterol, low-density lipoprotein cholesterol.[38] Some observations indicate that isoflavones available in soybean have an important role in decreasing blood cholesterol but some studies refute this. Moreover, proteins available in soybean may have more an important role compared with these flavones.[3]

Dosage. The US Food and Drug Administration recommends 25 g of soybean protein to decrease blood cholesterol, although consuming higher dose is more effective. Observations suggest that replacing 20 g of soy protein with meat protein decreases blood cholesterol significantly. Some studies prescribe 40 g daily.[32]

Drug Interaction. Soy may decrease the effect of thyroid drugs. Moreover, several evidences show that soy isoflavones can inhibit the performance of the thyroid gland, although this state may be only significant in individuals with iodine deficiency. Of course, some studies also reject the effect of soy and its isoflavones on thyroid hormones. Finally, individuals with thyroid problems are recommended to avoid high amounts of soy. Soy can decrease absorption of iron, calcium, and zinc. To compensate this state, materials containing these compounds should be used 2 hours after the consumption of soy.[32]

Toxicity. Although soy and its isoflavones can cause harmful effects in some conditions, animal studies have suggested that soy has no toxic effect.[18] Clinical studies suggest that soy decreases the level of the testosterone hormone in men. Moreover, some studies indicate the presence of estrogenic property in soy isoflavones. For this reason, use by pregnant women can lead to embryo damage.[32]

Silybum marianum L

The main components of *Silybum marianum* L extract is known as silymaryne. Silimaryne, consisting of 4 compounds including sylymarin, is a herbal drug with hepatoprotective properties and contains different compounds like flavonoids with antioxidant, cellular membrane stabilizing, and blood glutathione increasing properties, and its positive effect in improving different diseases including hyperlipidemia have been reported in laboratory studies.[39-41] Results of the clinical researches indicate that silimaryne can be presented as a blood cholesterol reducer in patients with hypercholesterolemia. Using 420 mg of silimaryne once a day decreased cholesterol concentration in bile in 15 patients with high blood cholesterol compared with the control group, indicating that cholesterol synthesis decreases in the liver.[42] In a clinical study performed on 14 patients with hypercholesterolemia type 2, silimaryne at a dose of 420 mg decreased the total cholesterol level and increased the blood high-density lipoprotein level. In a clinical study, administration of silimaryne to diabetic patients with the hyperlipidemia decreased the total cholesterol, low-density lipoprotein, and triglyceride levels.[42]

Red Yeast Rice

Red yeast rice is an important foodstuff in the daily diet of Chinese people. This is native to China and is the secondary product that results from the fermentation of a kind of cooked rice that red yeast rice has grown on it. This material is prescribed in traditional Chinese medicine as blood circulation and food digestion stimuli.[43] It has been reported that prescription of red yeast rice decreases blood cholesterol, and this effect is attributed to the statins available in this material. Statins are prescribed as blood cholesterol lowering drugs. Red yeast rice contains some active compounds including monacolin K, dehydromonacolin, and monacolin I-VI in addition to starch, protein, fiber, sterols, and fatty acids. Researchers have stated that one of the components of this yeast, monacolin K, inhibits production of cholesterol via stopping the activity of the HMG-CoA reductase enzyme, which has an important role in cholesterol synthesis. Statins are a class of hypocholesterolemic drugs

that reduce cholesterol levels by inhibition of HMG-CoA reductase in the liver. This enzyme is responsible for the production of more than 70% of total cholesterol in the body.[44]

Although the amount of monacolin K in red yeast rice is lower than lovastatin (2% in 5 mg vs 20-40 mg), it acts similarly. For this reason, researchers have proposed that red yeast rice contains other compounds like sterols that possibly have a role in decreasing cholesterol.[44] In addition to laboratory studies on animals, red yeast rice has been studied clinically in order to study its cholesterol-lowering effect. In a study, patients used daily 1.2 g of the concentrated extract of yeast (containing approximately 13.5 mg monacolin) for 2 months. In this study, significant decrease in the total serum cholesterol level was observed. Moreover, serum high-density lipoprotein level in these people increased and the low-density lipoprotein and triglyceride levels decreased.[45]

Dosage. A product called colistin obtained from this yeast has entered into the China market and its dosage is 1.2 to 2.4 g daily with divided doses for 8 to 12 weeks.[43]

Restrictions. People with liver disorders and pregnant women should not use red yeast rice. With regard to the similar effect of red yeast rice and statin drugs, they should be used together under the supervision of a physician.[43]

Toxicity. Usually, consumption of this material is tolerable and generally has no side effects, but some effects like heart burn and mild vertigo have been observed.[45]

Commiphora mukul (Guggul, Gugulipid)

Commiphora mukul is an adhesive gum that is obtained from the Mukul myrrh tree. In the traditional medicine of India, this material is combined with other plants and is applied to treat skin problems, nervous system pains, obesity, diabetes, digestive problems, rheumatoid pains, mouth infection, and menstrual problems.[46] To study the effect of this material on blood cholesterol, a study on 61 individuals was performed for 24 weeks. After 12 weeks of diet control, half of the individuals received placebo and other half received Guggul at 100 mg daily dose. After 12 weeks, the total cholesterol level decreased 11.7%, low-density lipoprotein level 12.7%, triglyceride 12%, and cholesterol-high-density lipoprotein ratio 11.1% in individuals who used Guggul, which was significant compared with the placebo group.[47] Moreover, a double-blind study performed on 228 individuals indicated similarity of this material's effect with that of clofibrate.[48] This multicentric, double-blind, crossover study was completed in 125 patients with Guggul and in 108 patients with clofibrate. None of the patients in the Guggul group showed significant side effect except one patient who showed some gastrointestinal symptoms, but not severe enough to necessitate withdrawal of the drug. Two patients in the clofibrate group showed flu-like syndrome and opted out of the study. In this clinical trial, which was conducted at Bombay and Bangalore, India, patients consumed *Commiphora mukul* in a dose of 500 mg 3 times per day for 12 weeks. The results showed a significant reduction in serum triglycerides (average 22.6%) and serum cholesterol (average 23.6%) in 70% to 80% of patients who consumed gugulipid. The average reduction in serum triglycerides and cholesterol was 16.8% and 11%, respectively, in patients who consumed with clofibrate. The lipid-lowering effect of both drugs became evident 3 to 4 weeks following the start of the drug. In this study, hypertriglyceridemic patients responded better to clofibrate; however, hypercholesterolemic patients responded better to gugulipid therapy. Clofibrate had no effect on high-density lipoprotein; however, high-density lipoprotein was increased in 60% of cases who consumed gugulipid. A significant reduction in low-density lipoprotein cholesterol was observed in the responders to both drugs.[48]

Dosage. Dosage depends on Guggul concentration and the level of the blood lipid, and usually 100 mg daily is prescribed.[46]

Toxicity. In clinical studies, no significant side effect has been reported after the administration of the standard extract of Guggul. Liver, renal, heart, and biochemical experiments indicate safe consumption of this material.[46]

Dietary Plants Fibers With Hypolipidemic Activity

Dietary fibers are complex carbohydrate polymers with plant origin that are composed of simple sugars and generally are classified based on solubility.[49] Soluble fibers are made up of sticky substances like gum pectin and mucilage that are readily consumed by the bacteria in colon. Insoluble fibers consist of structural and/or matrix fibers such as lignin, cellulose, and hemicellulose, which are digested without change. Useful effects of dietary fibers in lowering blood lipids have been reported in clinical and laboratory researches.[49]

Plantago psyllium

Plantago psyllium is water-soluble fiber derived from Plantago ovate seed husk. In a study conducted on individuals with hypercholesterolemia, 6 to 8 weeks of psyllium treatment decreased total cholesterol by 3.5% to 5.6% and low-density lipoprotein cholesterol by 5.1% to 8.8% compared with placebo treatment. In an experiment on 125 individuals with type 2 diabetes and hyperlipidemia, 5 g psyllium seed was taken 3 times per day for 6 weeks. In these patients, in addition to decrease in the blood glucose level, the total cholesterol, low-density lipoprotein cholesterol, and plasma triglyceride levels decreased after 2 weeks of treatment, while the high-density lipoprotein cholesterol level increased.[50]

In this study, the hydrophilic mucilloid of psyllium was examined in 75 hypercholesterolemic patients for its ability to lower serum cholesterol. Patients with mild to moderate hypercholesterolemia were included in this double-blind, randomized, placebo-controlled parallel trial. In step I, the patients

were treated with a diet for 12 weeks before receiving placebo or 3.4 g of psyllium 3 times/day for 8 weeks. Reported adherence to diet and treatment was high, and no significant adverse side effects were noted. In comparison to placebo, psyllium achieved an additional 4.8% reduction in total cholesterol level, 8.2% reduction in low-density lipoprotein cholesterol level, and 8.8% reduction in apolipoprotein B level, with no significant effect on blood pressure, serum glucose, or levels of triglycerides, high-density lipoprotein, or iron. The authors concluded that the hydrophilic mucilloid of psyllium was an effective and well-tolerated adjunct to diet in the management of mild to moderate hypercholesterolemia.[51]

Use in Pregnancy and Breast-feeding. No harmful side effects have been observed as a result of using the Plantago ovate seed or its seed husk, if the usual dose is used during pregnancy and breast feeding.[51]

Drug Interaction. Insulin-dependent diabetic patients may need to reduce the irinsulin dosage while using plantago ovate seed. The drug interaction between plantago ovate seed with lithium and carbamazepine has been reported. The simultaneous use of drug and plantago ovate seed may cause problems in drug intake. So it is recommended to use the seed of this plant ½ to 1 hour after the use of the drug. Plantago ovate seeds that are used mainly as emollient may cause subcutaneous emphysema. A large amount of water (not juice or other liquids) should be used to maintain the levels of water excreted. If there is no external water, plantago ovate seed absorb the water from wet mucous membrane of the gastrointestinal tract, which may lead to the damage of a part of bowel that is accompanied by intensive abdominal pain.[51]

Dose. The dose is 5 to 15 g of the seed husk but administration of 5 g of the seed husk to decrease the glucose level and blood lipid has been stated in a report.[52]

Cyamopsis retragonoloba (Guar Gum)

Guar gum is the nutrient derived from the edible seed of the *Cyamopsis retragonoloba* plant, which is an ingenuous plant of Asian countries. Laboratory studies showed that administration of guar gum to rat decreased the blood cholesterol level significantly in these animals. This effect was attributed to the effect of this dietary fiber on enterohepatic circulation. It has been stated that guar gum also decreases the fat intake available in foods by affecting the microflora of the gastrointestinal tract.[53] In addition, reports presented in other researches indicate that the lowering of blood cholesterol by guar gum is possibly due to the increase of steroids' excretion in feces and also increase of bile production.[54] It has been reported that administration of guar gum decreases appetite and in addition decreases cholesterol and triglyceride levels, and as a result weight of laboratory animals is decreased. In clinical studies also administration of guar gum to individuals with type 2 diabetes and hyperlipidemia decreased sugar and blood lipid levels.[54]

Dose. A dose of 15 g daily should be used to decrease cholesterol.[27]

Oat

Oats as a foodstuff containing high fiber, in addition to different nutritional properties, can decrease the blood cholesterol level. In a study, 152 patients whose low-density lipoprotein levels was between 120 and 190 and triglyceride levels lower than 400 were fed oat diet for 6 weeks and the total cholesterol and low-density lipoprotein levels decreased.[53] A study showed that diet containing oat has a positive effect on body metabolism of women who are overweight. Using oat also led to decrease in the cholesterol level and low-density lipoprotein levels of individuals with hyperlipidemia in this study. Moreover, it has been stated that antioxidant properties of oat inhibit low-density lipoprotein oxidation, dose-dependently.[54]

Dose. Dose for individuals with hyperlipidemia has been reported to be 28 g/day.[27]

Discussion

Hyperlipidemia has been shown to affect the antioxidant status of different organs as well as their lipoprotein levels.[55-57] Lipid-lowering medicinal plants may reduce hyperlipidemia, preventing atherosclerosis and vascular endothelium damage.[58,59] In most cases this effect and even the other effects of medicinal plants, at least in part, have been attributed to their antioxidant properties.[60-63]

Hyperlipidemia increases the production of free radicals, which in turn increases oxidative stress and low-density lipoprotein oxidation. During this process, low-density lipoprotein converts to oxidized low-density lipoprotein, induces the expression of adhesion molecules, stimulates activation of T cells and macrophages, increases the production of foam cells, and attracts macrophages to the sarcoplasmic reticulum. Oxidation of low-density lipoprotein has a crucial role in the formation of atherosclerotic plaques.[64,65]

Initially, lipophilic antioxidants preserve low-density lipoprotein particles against deformation, but in case of antioxidant deficiency unsaturated fatty acids will be oxidized. In this step of oxidation, low-density lipoprotein particles usually undergo slight changes. However, if this step continues and causes more accumulate of lipid oxidation products, these components start reacting with amino acids of ApoB-100 protein and cause covalent bond formation, resulting in increase in degradation of their protein part of low-density lipoprotein.[66-68]

Ox-low-density lipoprotein has a wide variety of effects such as chemokine expression, monocytes proliferation, chemotaxis of monocytes, fat cells formation, inhibition of macrophages movement, expression of endothelial adhesion molecules, growth factor stimulation,[69] fatty streaks formation,

and thickening of intima. All of these changes are effective in the progress of atherosclerosis.[70-73]

Inflammation is also related to coronary artery diseases. For example, C-reactive protein, which reflects extravascular inflammation, is increased in atherosclerosis and its complications.[7] It has been shown that patients with high C-reactive protein levels are also more prone to hypertension and diabetes mellitus, and both of these are related to atherosclerosis.[74] Reduction of free radicals by plants antioxidants, therefore, which scavenge free radicals and reduce oxidative stress, apart from reducing hyperlipidemia, can reduce the possibility of atherosclerosis.

Antioxidants such as beta-carotene, selenium, and vitamins C and E were considered as being able to prevent cell membrane oxidation.[75,76] However, recently their widespread use has been recommended to be limited because of their toxic effects or being ineffective. Therefore, natural compounds with antioxidant activity, which mostly have low toxic effects, seem to have beneficial effects.

In this regard, the Food and Nutrition Board decreased the recommended dietary allowance for some of these agents. Since the last report of the recommended dietary allowance, in 1989, the Food and Nutrition Board has changed the criteria for establishing recommended dietary allowances from prevention of deficiency diseases to prevention of chronic diseases. However, the revised recommended dietary allowances by the Panel on Dietary Antioxidants and Related Compounds of the Food and Nutrition Board were not based on the prevention of chronic diseases but based primarily on the prevention of deficiency symptoms. Hence, the new recommended dietary allowances for dietary antioxidants were different from the recommended dietary allowances published in 1989. The new recommended dietary allowances for adults are as follows: vitamin C, 75 mg/day for women and 90 mg/day for men; vitamin E, 15 mg/day or 22 IU for women and men; and selenium, 55 μg/day for women and men.[77]

The Panel considered the possibility that intakes higher than the recommended dietary allowances might prevent chronic diseases, but concluded that there were insufficient data to *prove* that increased intake of antioxidants exert beneficial health effects beyond the prevention of deficiency symptoms. The Panel established values for the upper intake level for dietary antioxidants too. The upper intake level is defined as "the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population." The upper intake levels for adult men and women are the following: 2 g/day for vitamin C, 1000 mg/day for vitamin E, and 400 μg/day for selenium.[77]

Herbal medicine extracts mostly have antioxidant properties.[78-81] Therefore, as a source of different antioxidants, they can be very effective in modulating oxidative stress, thus protecting different organs such as heart,[10] kidney,[82-86] and live,[87-89] from oxidative damages.[90-92]

Although different components of plants can have antioxidant effects, the main part of such effects is attributed to phenol compounds.[93-95] A lot of medicinal herbs such as *Ocimum basilioum*, *Allium sativum*, *Silybum marianum*, *Anethum graveolens*, *Boswellia carterii*, *Juglans regia*, *Trigonella foenum-graecum*, *Berberis vulgaris*, *Nigella sative*, *Sesamum indicum*, *Aloe vera*, *Ziziphus jujube*, and *Zingiber officinale* possess antioxidant activities thanks to their phenolic compounds.[18,66,96-102] Some of these plants have been examined for their hypolipidemic activities and the others are worth examining.

Conclusion

Today, hyperlipidemia and its resultant side effects have been known as one of the medicinal problems in most societies. Hyperlipidemia, in addition, intensifies metabolic disturbances and increases the risk of cardiovascular diseases, especially in patients with diabetes and blood pressure. Available information indicates that compounds available in food supplements and medicinal plants including dietary fibers, vitamins, flavonoids, sterols, and other antioxidants can be effective for the metabolism of lipids by influencing the metabolic reactions of different tissues. In most cases the lipid-lowering properties of these plants, at least in part, have been attributed to their antioxidant properties, and a lot of medicinal plants possess antioxidant properties.[103-106] Therefore, it might be useful to examine other medicinal plants that have antioxidant activities for their hypolipidemic activities.

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Ethical Approval

This study is exempt from oversight by human subjects research protection as there were no human subjects involved.

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